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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,352	01/14/2002	Renji Yang	0109015/024	4868

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BELL, BOYD & LLOYD, LLP
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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/047,352	YANG ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,23,25,31,33-35,39-44,46,49-51,54-56,58-64,66,67,69,70,81 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 6,23,25,31,33-35,39-44,46,49-51,54-56,58-64,66,67,69,70,81 and 82.

DETAILED ACTION

Response to Amendment

1. The amendment filed 1/17/07 has been entered.

2. The rejection of claims 31, 33-35, 39-44, 64, 66-67, 69-77 under 35 U.S.C. 112, first paragraph, for new matter is withdrawn due to either the amendment or cancellation of the claims, or due to Applicants' arguments.

3. The rejection of claim 77 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn due to the cancellation of this claim.

4. The rejection of claim 6, 23, 25, 31 & 33-35, 39-44, 46, 48-51, 54-57, 58-64, 66, 67 & 69-77 under 35 U.S.C. 102(b) as being anticipated by Nakafuka et al (IDS Ref #26) is withdrawn solely because of the amendment of the claims to "human neural precursor cell line", or due to the cancellation of the claims. Note that claims 25 & 33 reasonably are limited to "human" neural precursor cells, as recited in base claims 23 & 31, respectively.

5. The rejection of method claims 51-52, 54-56, 58-64, 66-67 & 69-77 under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Eilers et al (IDS Ref #20) and/or Evans et al (1988) is withdrawn due to the amendment of the claims to require "expanding the neural precursor cell including the c-myc construct beyond thirty cell

doublings prior to differentiation of said cell", or due to the cancellation of the claims, and because of the Johe Declaration under 37 CFR 1.132 filed 1/18/07 is sufficient to overcome the rejection of these method claims under 35 USC 103. However, it is suggested that the recitation of "wherein said cell resists differentiation" be deleted or changed in base claim 64 to "does not differentiate" to reflect a clearer and better defined invention.

6. Applicant's arguments filed 1/17/07 have been fully considered but they are not deemed to be persuasive.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 6, 23, 25, 46, 49-51, 54-56, 58-63 & 81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper NOs: 20060104 & 20060713, and as follows. Note that this is a new matter rejection.

Applicants argue on pages 9-12 of the response how various recitations in the claims have proper support. Applicants' arguments are persuasive as it relates to "retinoid receptor", "nuclear receptor", "wherein the second [listed] mitogen is different from the first mitogen", and "neural precursor" "clonal cell line". However, Applicants ignore the basis of the remaining new

matter rejection. As previously made of record, it is improper to broaden what the specification actually discloses in order to create a new genus of claims after-the-fact; thereby, constituting new matter.

In particular, the proper context for "portions" or "proportions" is not any generic or undefined "proportion", but specific "%[s] of the total cells" that express specifically described markers, and additionally, only as it relates to using the MycER construct, versus any broader concept of using any generic "nuclear receptor ligand-regulated *c-myc* gene", or for generically having "at least 20% of said neural precursor cells... capable of differentiating..." (i.e., as it relates to claims 23, 25, 46, 49, 50, 51, 54-56, 58-63 & 81); thereby, still constituting new matter. Likewise, Applicants have not totally amended all claims, as it relates to "resists differentiation in media containing a mitogen" **and β-estradiol** (e.g., see page 10 of the specification and page 10 of the response), or alternatively, wherein **β-estradiol** is "substitute[d]" by the appropriate "nuclear receptor" "ligand" (see page 26, lines 1-3 of the specification and page 10 of the response), versus only a "mitogen" being contemplated in this method (i.e., as it still relates to claims 6 & 44); thereby, still constituting new matter.

9. Claims 6, 23, 25, 31, 33-35, 39-44, 46, 49-51, 54-56, 58-64, 66-67, 69-77 & 81-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper No: 20060104, and as follows.

As previously made of record and in contrast to Applicants' arssertions on page 12 of the response, no written description of any "c-myc ***gene***" with its structurally definable 5'- and 3'-flanking regions, etc. is described within the instant specification. See again MPEP 2163, as it relates to written description for "genes". In other words, deletion of the recitation of "gene" may obviate this rejection, for the reasons previously made of record. In contrast, constructs using the well known human c-myc cDNA should have sufficient written description.

10. Claims 25, 33 & 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

No antecedent basis now exists for "mammalian" in base claims 23 & 31, respectively.

Claim 49 is dependent on a cancelled base claim 48.

11. Claims 6, 23, 25, 31, 33-35, 39-44, 46 & 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Eilers et al (IDS Ref #20) and/or Evans et al (1988), for the reasons made of record In Paper NOs: 20050124 & 20060713, and as follows.

Applicants argue on page 13 of the response that "[t]here is no discussion in Nakafuku of preventing differentiation and transformation of the cells based upon the amount of β-estradiol added to the culture media in order to stabilize the cells", and neither do Eilers nor Evans. However, in contrast to Applicants' assertions, no structurally definable amount of β-estradiol is recited in the claims to distinguish the claimed products from that of Nakafuka et al, in view of

Eilers and/or Evans et al. As previously made of record, Applicants' arguments remain not persuasive for those "product" claims 6, 23, 25, 31, 33-35, 39-44, 46 & 49-50, especially when Nakafuka et al teach *in vitro* stable cultures of rat/mammalian neural precursor cells transfected with the same *mycer* construct as used in the instant application, which is further recited in the instant claims; thereby, still being consistent with that held by the courts in *In re Thorpe, In re Marosi, Ex parte Gray, In re Best*, and *In re Brown* previously made of record.

The Johe Declaration under 37 CFR 1.132 filed 1/18/07 is insufficient to overcome the rejection of the product claims under 35 USC 103, as set forth in the last Office action because motivation does not need to be the same as proposed in this declaration, nor does the same method need to be used to generate an identical product (i.e., neural precursor cell line containing MycER). Clearly, the previous Office action establishes a *prima facie* case for obviousness for making a human neural precursor cell line containing MycER, as extensively made of record.

In summary, Nakafuka et al teach *in vitro* stable monolayer and suspension clonal cultures of rat/mammalian neural precursor cells (which are at least initially cultured in the presence of unmodified cells/incomplete transfections) using the same *mycer* construct as used in the instant application (i.e., c-myc proto-oncogene cDNA construct fused to the ligand binding domain of an estrogen receptor selectable marker; pgs. 155, 156, 162 & Table 1; as it relates to claims 6, 23, 31, 39, 43, 44, 46 & 49); thereby, establishing the clonal cell line, MNS-57. These MNS-57 cells maintain a multipotential capacity to differentiate into neurons, astrocytes and oligodendrocytes/glial (e.g., pgs.153, 154, 159-160 & especially162 (2nd col.); as it relates to claims 23, 25 & 34-35). It is noted that the method of producing these cells using various

mitogens, such as bFGF or EGF or β-E_2 (e.g., pgs 155-156 & 157-162) does not change the inherent properties of these claimed precursor/stem cell **products** (i.e., as it relates to claims 6, 31 & 40); especially when CNS neural stem cells are inherently and naturally derived from pluripotent embryonic stem cells (i.e., as it relates to claims 25 & 33), and structurally and functionally possess the same inherent properties no matter what region within the brain from which they are derived (i.e., as it relates to claims 25, 33, 41-42 & 50); absence evidence to the contrary. However, Nakafuka et al do not teach human neural precursor cell cultures containing a MycER construct.

Eilers et al. teach both the c-myc construct used above by Nakafuka et al., as well as a similar c-myc construct, *mycgr*, contains the sequence that encodes the hormone [ligand] - binding domain of the rat glucocorticoid receptor fused to the 3' end of *myc* transforms these cells in a glucocorticoid-dependent manner (pg. 67, 1st *pp*; as it relates to other ligand binding domains in claims 23, 31, 43, 48 & 49). However, although Eilers use a human myc construct, they do not specifically teach a stable culture of human neural progenitor cells.

Evans is a review describing the well known ligand binding domains of steroid/thyroid hormone receptors (e.g., pg. 891; as it relates to estrogen, androgen, progesterone, glucocorticoid, thyroid hormone, retinoid and ecdysone receptors and their respective ligands/myc-activating chemicals in claims 23, 31, 43, 48 & 49). However, Evans does not teach stable cultures of human neural progenitor cells transfected with a c-myc construct.

It would have been obvious to one of ordinary skill in the art to produce stable mammalian/human neural precursor cells, as taught by Nakafuka et al., using any well known steroid/thyroid hormone receptor ligand binding domain, as taught by Evans, fused to Eilers' c-

myc constructs, because Eilers et al teach that "similar chimaeras" transform cells in a steroid/ thyroid hormone-dependent manner, and because of the potential human neural stem cells specifically possess in treating neurological disease states by replacing neural tissue that no longer exists, and by eliminating/minimizing host immuno-rejection of neural stem cells from non-human species.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
April 12, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER